



NOVEL INDOLE CONTAINING THIAZOLIDINEDIONE DERIVATIVES AS POTENT EUGLYCEMIC AND HYPOLIPIDAEMIC AGENTS

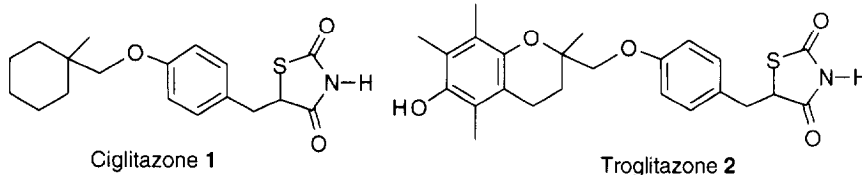
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Abstract: Several thiazolidinediones having indol as heterocyclic moiety have been synthesized and evaluated for euglycemic properties. A few of them have been found to be superior to troglitazone.

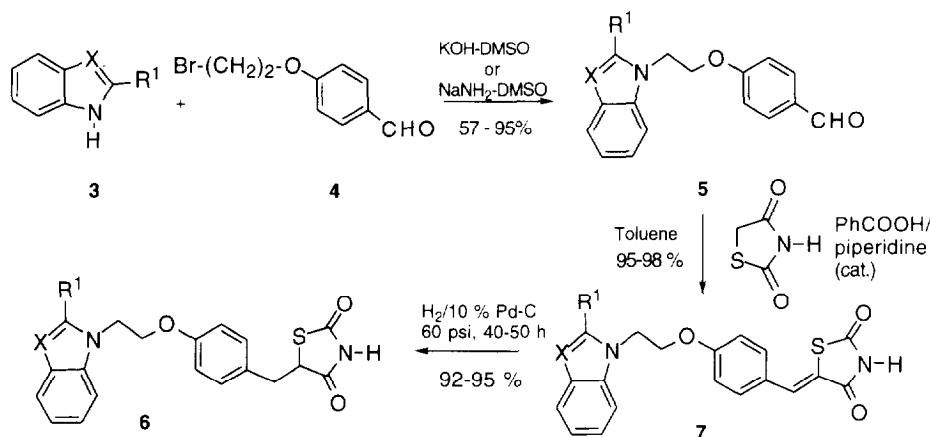
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During the last decade the search for a new class of compounds having euglycemic activity for the treatment of Non-Insulin-Dependent-Diabetes Mellitus (NIDDM), typically characterized by peripheral insulin resistance, hyperglycemia, hyperinsulinemia, has gained considerable importance.¹ It has been reported that sulfonylureas, the most commonly used oral hypoglycemics, potentiate insulin action in peripheral tissue² but mainly stimulate insulin secretion from β -cells which might bring about undesired side effects such as hypoglycemia. Consequently, there is need for new therapeutic options which do not involve increasing circulating insulin concentration.³



In preclinical rodent models of obesity, insulin resistance and hyperglycemia, thiazolidinediones ameliorate insulin resistance and normalize plasma glucose and plasma insulin without causing hypoglycemia even at very high doses.⁴ The discovery of ciglitazone **1**,⁵ has spurred uninterrupted interest in this class of compounds with greatly improved *in vivo* potency.⁶ Hulin *et al.* have recently published an excellent review compiling the recent status of insulin sensitizers in NIDDM model.⁷ However, due to unsatisfactory efficacy and safety profile of these agents in preclinical testing,⁸ none of the thiazolidinedione class of compounds has reached the market so far. Only recently the first candidate troglitazone **2** has been registered for launching in Japan.⁹ Presently, various non-thiazolidinediones analogs are also being tested for their insulin sensitizer activities.¹⁰ Some of the tryptophan derivatives have been reported to lower the blood glucose following a single dose in KKAY mice (dose : 50 mg / kg).^{11,12} Tryptophan being a commonly occurring amino acid in human beings might show an improved toxicity profile.¹³ Thus, we synthesized several thiazolidinediones having tryptophan and indole moieties and tested for their euglycemic activities.

In the present communication we describe the preparation of several thiazolidinediones having tryptophan or indole moieties and their euglycemic activities in *db/db* and *ob/ob* mice. The compounds reported in the Table-1 were synthesized by alkylation of the appropriate heterocycle **3** with 4-(2-bromoethoxy)benzaldehyde **4** as shown in scheme 1 to give 57-95 % of aldehyde **5**. The aldehyde **5** was treated with thiazolidinedione in the presence of piperidinium benzoate in refluxing toluene with azeotropic removal of water to give excellent yield (95-98%) of **7**. Finally, thiazolidinedione **7** was reduced to **6** by hydrogenation in the presence of Pd-C (10 %) at 60 psi of hydrogen at *ca* 25 °C in dioxane during 40 - 50 h. Usually, 1.2 to 1.5 equivalent of Pd-C (10 %) is required for the hydrogenation of **7** to **6**, which might be attributed to the poisoning of Pd-catalyst due to thiazolidine moiety. The reduction of **7** to **6** can also be affected using magnesium (17.0 eq) in methanol for 6 h at *ca* 30 °C.¹⁴



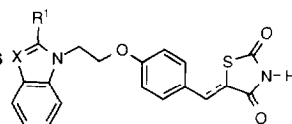
Scheme 1

Biological evaluations The antidiabetic activities of compound **6** and **7** were tested in 8 - 12 weeks old C57BL/KJ *db/db* mice and 10 week old C57BL/6J *ob/ob* mice obtained from Jackson Laboratories, U.S.A. The compounds were fed *via* oral gavage at a dose of 100 - 200 mg / kg. Blood samples were collected on 0, 3rd, 6th and 9th days and were analysed for blood sugar. The results are shown in the Table - 1. In the biological test, a group of 4 - 5 animals (male or female) were used with a vehicle control and troglitazone (200 mg/kg p.o.) as standard for comparison. At the end of the 9th day, the % reduction in triglyceride level was calculated and in few cases, mice were subjected to oral glucose tolerance test. From table 1 it is clear that several compounds showed similar or better blood glucose and triglyceride lowering activities than troglitazone. We have selected compound **6c** for a detailed evaluation in *db/db* and *ob/ob* mice at various doses. In *db/db* mice, compound **6c** produced 60 - 70 % reduction in blood glucose level after 3 days treatment even at 50 mg / kg dose. Similarly, in *ob/ob* mice, a dose of 20 mg / kg was sufficient for normalizing the blood glucose level. These results indicate that compound **6c** is far superior euglycemic and hypolipidaemic agent than troglitazone. Compound **6c** also showed considerable reduction of cholesterol level in blood.

Conclusion: Thus, we have been able to prepare a thiazolidinedione with greater potency/efficacy compared

to troglitazone. Further studies of these compounds for toxicity, bioavailability, stability *etc.* are under progress and will be reported later.

Table - 1 : Thiazolidinedione 6 and 7 and their Biological Activities



Compound No.	R ¹	X	Dose mg/kg	Redn. in % RBS ^a 3, 6,9 days	% Redn. in AUC ^b	% Redn. in TG ^c
6c	H	CH	200	64,68,74	55	77
6e		4,5-Benzo-	100	0,0,0	ND	21
7a	H	$\begin{array}{c} \text{CCH}_2\text{CHCOOH} \\ \\ \text{NH}_2 \end{array}$	100	0, 29,0		64
7b	COOH	CH	200	50,39,12	ND	0
7c	H	CH	200	27,40,33	15	37
7d	H	N	200	22,31,33	ND	76
7e		4,5-Benzo-	100	0,0,0	ND	44
Troglitazone	-	-	200	14, 16,24	20	50

(a) % Redn. in RBS = Random Blood Sugar was measured on 0, 3rd. 6th and 9th days, % reduction was calculated. (b) % Redn. in AUC = Glucose tolerance test (GTT) was performed 24 h after withdrawal of drugs. GTT was performed on 18 h fasted animals after feeding 3 g / kg of Glucose. (c) TG = Triglyceride were measured on 0 and 9th day. ND = Not determined.

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14. All the compounds were fully characterized. Structural data for **6c** is presented here: mp 103 °C; ^1H NMR (CDCl_3) δ 8.18 (bs, 1 H), 7.65 (d, J = 7.4 Hz, 1 H), 7.39 (d, J = 8.30 Hz, 1 H), 7.30 - 7.15 (m, 2 H), 7.08 (d, J = 8.72 Hz, 2 H), 6.76 (d, J = 8.72 Hz, 2 H), 6.50 (d, J = 2.92 Hz, 2 H), 4.50 (t, J = 5.52 Hz, 2 H), 4.43 (dd, J = 9.45, 3.75 Hz, 1 H), 4.23 (t, J = 5.52 Hz, 2 H), 3.39 (dd, J = 14.11, 3.74 Hz, 1 H), 3.04 (dd, J = 14.11 and 9.45 Hz, 1 H); ^{13}C NMR (CDCl_3) δ 174.64, 170.95, 157.64, 135.99, 130.28, 128.57, 128.32, 128.17, 121.58, 121.00, 119.48, 114.72, 109.16, 101.59, 66.77, 53.56, 45.52, 37.50; Mass m/e : M^+ = 366.